



Important Doctors slides
Extra Information Doctors notes

Biochemistry

Metabolic Syndrome



[Editing file](#)

“ There is nothing permanent except change. ”
- Heraclitus



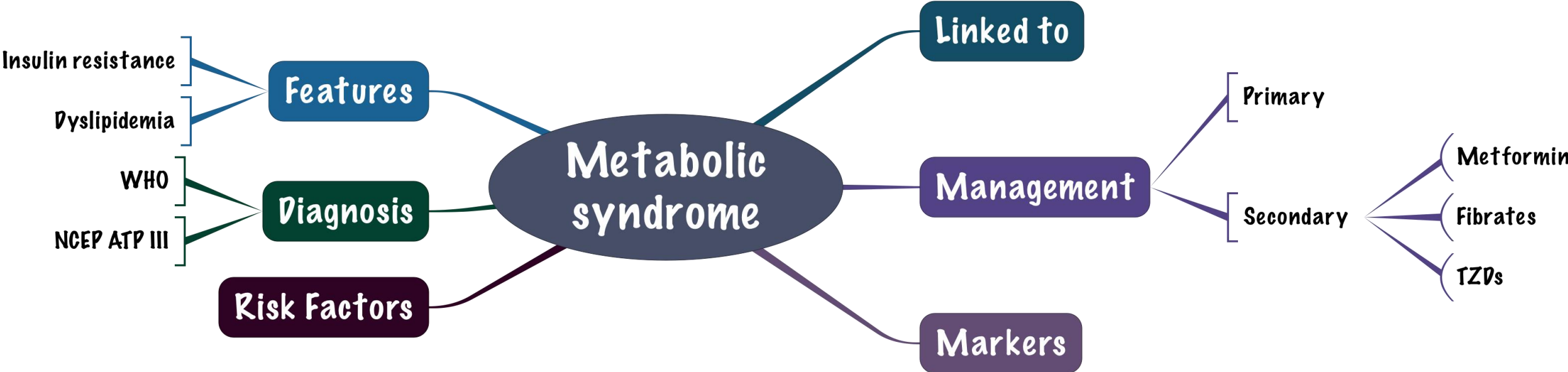
OBJECTIVES

By the end of this lecture, the students should be able to:

- Define metabolic syndrome, insulin resistance and dyslipidemia
- Discuss the risk factors for metabolic syndrome and other medical conditions associated with it
- Define the diagnostic criteria for Metabolic syndrome
- Discuss the management of metabolic syndrome and current treatment options



Overview



Metabolic Syndrome

- It is a combination of metabolic abnormalities which increase the risk of heart disease, diabetes and other diseases.

Metabolic syndrome by itself isn't a disease, They are metabolic abnormalities that considered as risk factor. All these risk factors put together, they were given different names before metabolic syndrome like: syndrome X, insulin resistance syndrome etc.. Metabolism syndrome starts with obesity, leading to other problems.

Features of metabolic syndrome

Visceral **Obesity**

High serum triglycerides (TGs)

Low HDL cholesterol

Hypertension

Hyperglycemia

Insulin resistance (hyperinsulinemia)

- Obesity is a component of metabolic syndrome **It has to be there**
- Molecular signals originating from the increased mass of adipocytes are predominantly reflected in the following metabolic abnormalities: **The more metabolic abnormalities present the higher the risk to develop disease are there**
- 1. Dyslipidemia . 2. Glucose intolerance .
- 3. Insulin resistance. . 4. Hypertension .

Insulin Resistance



- **Hydrolysis** of stored fats → high plasma FFAs
- **Reduction** of glucose uptake/use by **cells (muscle)**
- **Reduction** of glycogenesis → **hyperglycemia**
- **Compensatory hyperinsulinemia** causes **down regulation** of insulin receptor
- **Defects in insulin receptor**

- As an obese person There's a high amount of lipids, which getting oxidized so, we need more insulin to function and maintain glucose level. Obese people eat more and have a much higher glucose level in their body. To bring it down slowly the body requirements of insulin become more and more, usually the body is still able to maintain the low normal glycemic state but later on, the glucose and lipid start targeting B-cells of pancreas and insulin production declines. That's why people who have DM type 2 for years eventually take insulin, it affects insulin receptor also causing insulin resistance.

Explanation

- ❖ When there's low level of insulin it affects the enzymes that required in glycogenesis. All of this with glucose present in the blood that is not taken up by muscles and adipose tissue and the glucose going to the liver isn't used for glycogen synthesis but it goes out from the liver.
- ❖ Even if the glycogen synthesis is working fine, there's a limit of how much glycogen can be stored in the liver only 5% of the liver's mass and after this limit it automatically shut off so we can't have overload of glycogen, and the rest of glucose is resented into the circulation again. All of this contribute to make **hyperglycemia**

- ❖ How obesity cause **insulin resistance**?
- ❖ When a person is obese, initially adipocytes or adipose tissue are storage for TAGs, whatever excess of carbohydrates or fat, are all stored in adipocytes. It's not just for storage it's an endocrine organ releasing a whole lot of hormones and other molecules some of them are adiponectin, lectin, resistin, IL-6, IL-1B and a lot more cytokines. All these put together and called adipokines, most of these molecules are pro-inflammatory molecules So, obesity can be considered as a Low grade chronic inflammation.
- ❖ All these signals coming from adipocytes cause a metabolic abnormalities such as **dyslipidemia, glucose intolerance, insulin resistance and hypertension.**

Dyslipidemia

Dyslipidemia

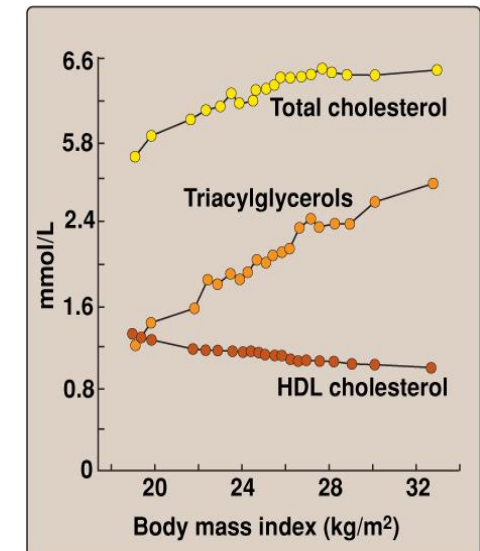
1. Insulin resistance in adipocytes	2. Increased insulin production to maintain blood glucose levels
3. Increased activity of hormone-sensitive lipase	4. high plasma FFAs
5. Carried to liver and converted to TGs/cholesterol	6. Excess TGs/cholesterol are released as VLDL in the blood
7. HDL are decreased	
<p>Dyslipidemia & Metabolic Syndrome relationship :</p> <ul style="list-style-type: none"> • Dyslipidemia is an early and consistent indicator of insulin resistance .If a person has insulin resistance he definitely has dyslipidemia • Liver fat plays a major role in dyslipidemia due to insulin resistance 	

So when insulin decreased we have 2 things are happens,

- 1- lipoproteins in the blood can't be broken so we aren't able to uptake the TAGs and can't clear the load from the blood.
- 2- the TAGs in the adipocytes that are broken down are going back into the liver and get repackaged into VLDL and resent back to the blood, so now the blood have a high amount of VLDL in the blood causing hyperlipidemia

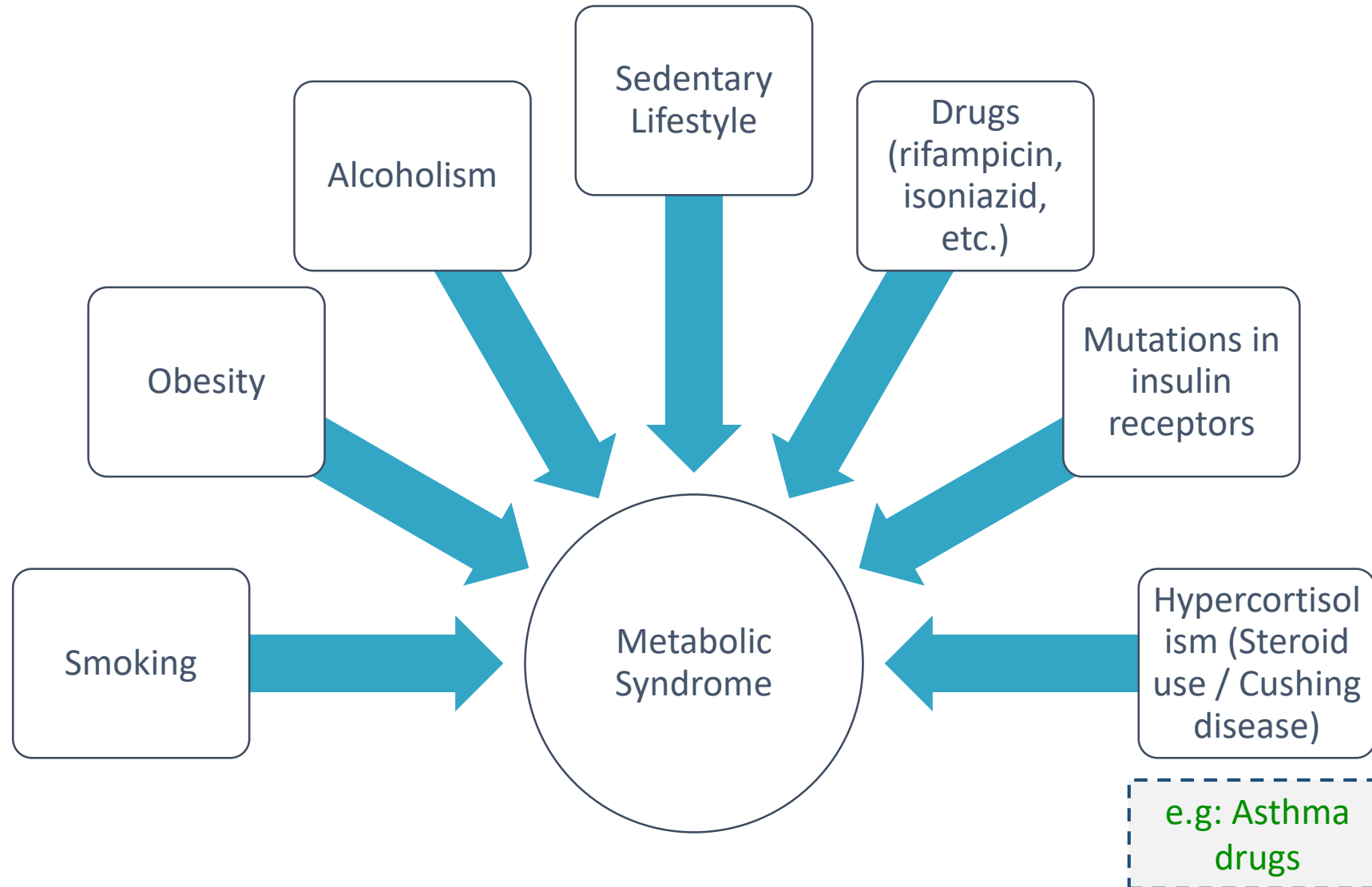
We have lipoprotein lipase which is in the plasma . Lipoprotein lipase cleaves the proteins that carries lipids that required for the cells (we have to cleave the proteins from the lipids to make cells take the lipids), its function is inhibited when insulin is low or there's insulin resistance.

Another enzyme we have is hormone sensitive lipase when insulin is low the activity of this enzyme goes up causing breaking of TAGs stores in adipocytes,



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Risk factors for Metabolic Syndrome



Metabolic Syndrome is linked to:

Metabolic syndrome	
Reproductive abnormalities	<ul style="list-style-type: none"> • Polycystic ovarian syndrome • Impaired ovulation and fertility • Irregular menstruation
Cancer Related to obesity	<ul style="list-style-type: none"> • Obesity is major risk factor for cancer of esophagus, colon or rectum, liver, gall bladder • Being overweight and obese accounts for 14% of all cancer deaths in men and 20% of those in women
Nonalcoholic steatohepatitis	<p>related to impaired lipid metabolism</p> <p>All fat goes to liver (when there is a lot of fat in the liver we call it steatosis) which leads to recruitment of macrophages after that Kupffer cells release their cytokines leading to NASH; which related to impaired lipid metabolism its frequency increases in metabolic syndrome</p>
Type-2 diabetes mellitus	5-fold increase Insulin resistance. ultimately develop into type 2 Diabetes
Heart disease	1.5 - 3 fold increase in atherosclerosis
Kidney disease	-

Diagnosis

WHO criteria (1999):

One of the following:

- Impaired glucose tolerance Prediabetes
- Diabetes mellitus
- Insulin resistance

PLUS two of the following: Any one of the above + any 2 from the table

Component	Criterion
Hypertension	BP >140/90 mmHg
Dyslipidemia	High plasma TGs (>1.7mmol/L) Low HDL cholesterol (men <0.9, women <1.0 mmol/L)
Central or General obesity	Waist to hip ratio >0.9 in men, >0.85 in women And/or BMI >30
Microalbuminuria	Urinary albumin excretion rate \geq 20ug/min or albumin:creatinine ratio \geq 30mg/g

not all obese people have insulin resistance, and there some people who have normal weight have insulin resistance

We don't go with BMI a lot because we focus on waste circumference; we care about visceral fat more than BMI

Diagnosis

NCEP ATP III Guideline (2002)

If any **3 or more** of the following risk factors are present:

- ✓ **Waist circumference:**
 - Men >102 cm (>40 in)
 - Women >88 cm (>35 in)
- ✓ **Triglycerides >150 mg/dL**
- ✓ **HDL cholesterol:**
 - Men <40 mg/dL
 - Women <50 mg/dL
- ✓ **Blood pressure 130/ 85 mm Hg**
- ✓ **Fasting glucose >100 mg/dL**

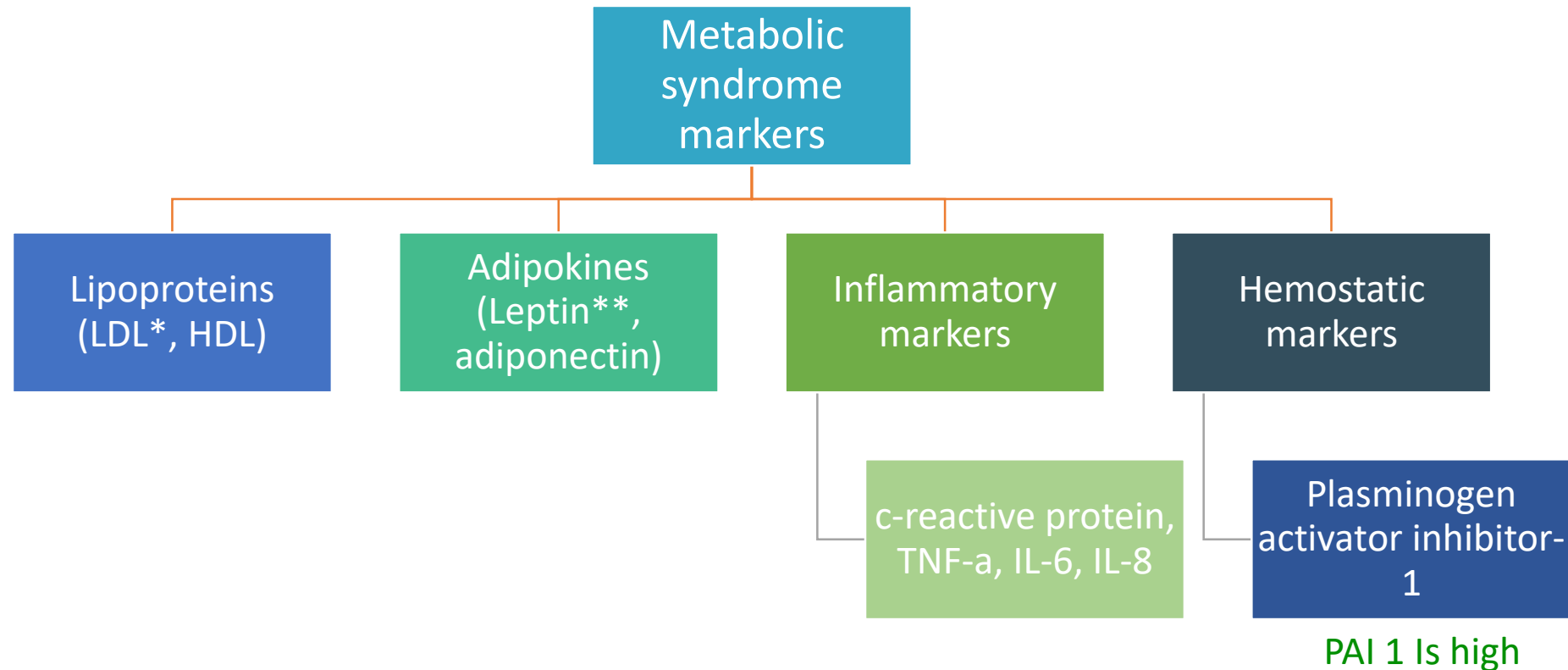
*NCEP: National Cholesterol Education Program

*ATP: Adult Treatment Panel

Don't memorize the numbers for the exam you'll be asked about the criteria that involved?

WHO focused on insulin resistance while here they focused on those five a person can be classified with metabolic syndrome even if he's not glucose impaired"

Markers of Metabolic Syndrome



Usually we don't measure insulin a lot rather than we measure insulin sensitivity by a rule:

HOMA-IR = amount of glucose X amount of insulin / 22.5

If 1.9 < early resistance, 2.9 < significant resistance

* LDL should be high HDL should be low

** Initially leptin is high but with progression of obesity it'll decrease to be normal and adiponectin will be low

Managing Metabolic Syndrome

Primary intervention:

- Lifestyle changes

Weight reduction

It will increase insulin sensitivity and decrease blood pressure

1- Target BMI < 25

2- Reduced intake of calories and fats

3- More physical activity

Smoking cessation

Because Smoking is a risk factor for a lot of other diseases like cardiovascular disease it increases BMR that's why smokers have less bodyweight than non smokers. Heavy smokers have more body weight than light smokers because of an unknown mechanism but what we know is that it affects fat deposition and increases visceral fat distribution in abdominal region that's why they have more weights and waist circumference and less muscle mass in the hips.

Managing Metabolic Syndrome

Secondary intervention:

- Medication to treat existing risk factors

Management of:

1- Blood pressure
(anti-hypertensive drugs)

2- Lipids
(statins, fibrates)

3- Blood glucose
(metformin, TZDs*)

Aspirin for
CVD**
prevention

Statins are anti cholesterol ; they inhibit HMG CoA reductase which is a rate limiter for cholesterol synthesis and that's how it lowers cholesterol.

*Thiazolidinedione

**Cardiovascular disease

Lowering blood pressure

Without using drugs

Modification	Recommendation	Average drop in SBP*
Weight loss	Maintain normal body weight	5-10 for every 22lbs loss
Healthy eating plan	Meals rich in <u>fruits, vegetables</u> ; <u>low fat dairy</u> ; low saturated fats and cholesterol	8-14
Sodium restriction	< 2400 mg/day	2-8
Regular physical activity	30 min. most of the week	4-9

*Systolic blood pressure

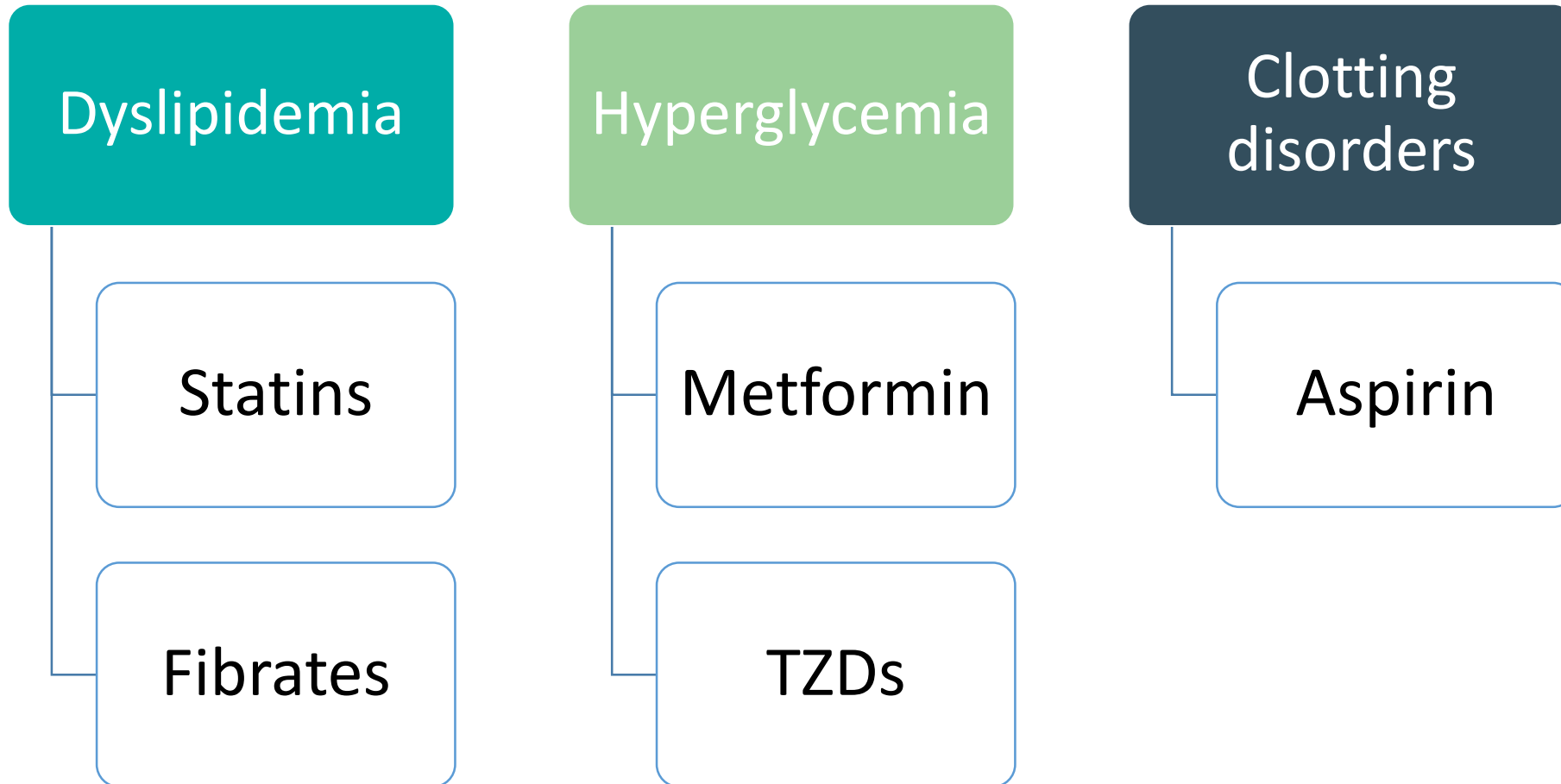
Lowering blood pressure

Hypertension and clotting disorders (by drugs)

Hypertension	Clotting disorders
Treat hypertension to goal (<130/80 mmHg)	Aspirin
Low dose diuretics	Daily low dose aspirin (81-325mg) for: <ul style="list-style-type: none">• Men > 45• Postmenopausal women
ACE Inhibitor (Preferred in diabetics)	

If his body weight is high or he has a high tendency to familial metabolic diseases, they're put on aspirin

Current Treatment



Metformin

Metformin	
Used to	<ul style="list-style-type: none">• Reduce blood glucose levels• Reduce blood lipids
Mechanism of Action	<p>Reduces blood glucose levels by inhibiting hepatic gluconeogenesis</p> <ul style="list-style-type: none">▪ Hepatic gluconeogenesis is active in patients due to liver's resistance to the effects of insulin <p>Reduces lipid synthesis in the liver</p> <p>→ Helps reducing blood lipids (Helpful with dyslipidemia also)</p>

When there's insulin resistance (the cell can't take up the glucose) the body perceives starving mode and the liver starts gluconeogenesis to make glucose which is a way to get hyperglycemia.

If we give metformin to obese person who doesn't have diabetes, it can lower body weight by decreasing lipid synthesis and blood glucose

Fibrates

- ❖ **Used to:** Reduce blood lipid level
 - ❖ **Mechanism of Action:**
 - ✓ Activate transcription factor :
 - Peroxisome proliferator activated receptor- α (PPAR-a)
 - ❖ Activated **PPAR- α** \rightarrow transcription of genes of **lipid degradation / uptake by the cells:**
 - **Carnitine** : palmitoyl transferase I (enhances FA uptake into mitochondria)
 - **Lipoprotein Lipase** (Explained at slide 7)
 - Stimulates **apoA1** and **apoAII** protein synthesis (major proteins in HDL)
- Increase production of HDL

This Transcription factor present mainly in the liver, When PPAR- α is activated it affects transcription of genes for lipid degradation or uptake by cells
how is that? this transcription factor increases the molecules and protein required for this process.

Thiazolidinediones (TZDs)

Thiazolidinediones	
Indication	<ul style="list-style-type: none">Used for the treatment of insulin resistance and type-2 diabetes mellitus
Mechanism of Action	<ul style="list-style-type: none">TZDs activate PPAR-g class of transcription factors expressed primarily in the adipose tissueActivates the transcription of adiponectin → Adiponectin reduces the fat content of the liver and enhances insulin sensitivity

SUMMARY:

Metabolic Syndrome	it is a combination of metabolic abnormalities which increase the risk of heart disease, diabetes and other diseases.
Features of metabolic syndrome	1-Hyperglycemia 2-Hyperinsulinemia 3-Low HDL cholesterol 4-Obesity 5-Hypertension 6-High serum Triglyceride
Risk factors for metabolic Syndrome:	1-Obesity 2-Alcohol 3-Drugs (Isoniazid, Rifampicin) 4-Sedentary lifestyle 5-High cortisol level 6-Mutation in insulin receptor
Metabolic Syndrome is linked to:	1-Heart disease 2-Kidney disease 3-Cancer 4-DMT2 5-Non alcoholic steatohepatitis
Metabolic syndrome markers	Lipoproteins (HDL, VLDL), Adipokines (Leptin, Adiponectin), Inflammatory markers and haemostatic markers
Managing metabolic syndrome:	Life style medication

SUMMARY:

WHO Criteria

One of the following:

- Impaired glucose tolerance, Diabetes mellitus and Insulin resistance
- PLUS two of the following:
- Hypertension, dyslipidemia, microalbuminuria, obesity

NCEP ATP III Guideline (2002)

If any 3 or more of the following risk factors are present:

- ✓ Waist circumference:
- ✓ Triglycerides
- ✓ HDL cholesterol
- ✓ Blood pressure
- ✓ Fasting glucose

QUIZ

Q1 : Which one of the following is correct in metabolic syndrome?

- A. High Serum TGs
- B. High HDL
- C. Hypoglycemia
- D. Glucose tolerance

Q2 : Which one of the following is correct about insulin resistance?

- A. Cells have an increased response to insulin
- B. High plasma FFA
- C. Low plasma Insulin
- D. Hypoglycemia

Q3 : Which one of the following is the unifying factor (common factor) between dyslipidemia and insulin resistance?

- A. Liver fat
- B. Hyperglycemia
- C. Smoking
- D. Hypertension

Q4 : Which one of the following is a marker for metabolic syndrome?

- A. Low LDL
- B. Increased Adiponectin
- C. High IL-6
- D. Decreased Leptin

Q5 : Which one of the following is a good management plan for hypertension?

- A. Low dose diuretic
- B. Aspirin
- C. Statins
- D. Metformin

Q6 : Which one of the following is correct about a goal for treatment of hypertension in terms of blood pressure?

- A. Blood pressure > 140/90 mmHg
- B. Blood pressure < 130/80 mmHg
- C. Blood pressure < 110/60 mmHg
- D. Blood pressure < 100/50 mmHg

QUIZ

Q7 : 60 year old woman came to your clinic with her daughter who is a medical student.(same girl in lecture 3)

She says that she is worried about her mother because she is obese and has hypertension.

But because she knows you're a good doctor, she wanted to confirm a few things with you

A) What other features may compromise metabolic syndrome?

Hyperglycemia, Low HDL, Hyperinsulinemia, high serum TGs,
Hypertension & obesity.

B) What are the risk factors for metabolic syndrome?

Smoking, Obesity, Alcoholism, Sedentary lifestyle,
hypercortisolism & mutation of insulin receptors.

C) What is the management of metabolic syndrome?

Primary intervention: Smoking cessation and weight reduction

Secondary intervention by pharmacotherapy:

For hypertension and clotting disorders: Anti hypertensives and aspirin.

For hyperglycemia: Metformin and Thiazolidinedione (TZDs)

For Dyslipidemia: Statins and Fibrates

*Suggestions and
recommendations*

1) A 2) B 3) A 4) C 5) A 6) B



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THANK YOU

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